10th POSTGRADUATE
Lymphoma
Conference

BTK Degraders: update of the results and their role in combination

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Venice,
March 12-13, 2026

Hotel Monaco & Grand Canal

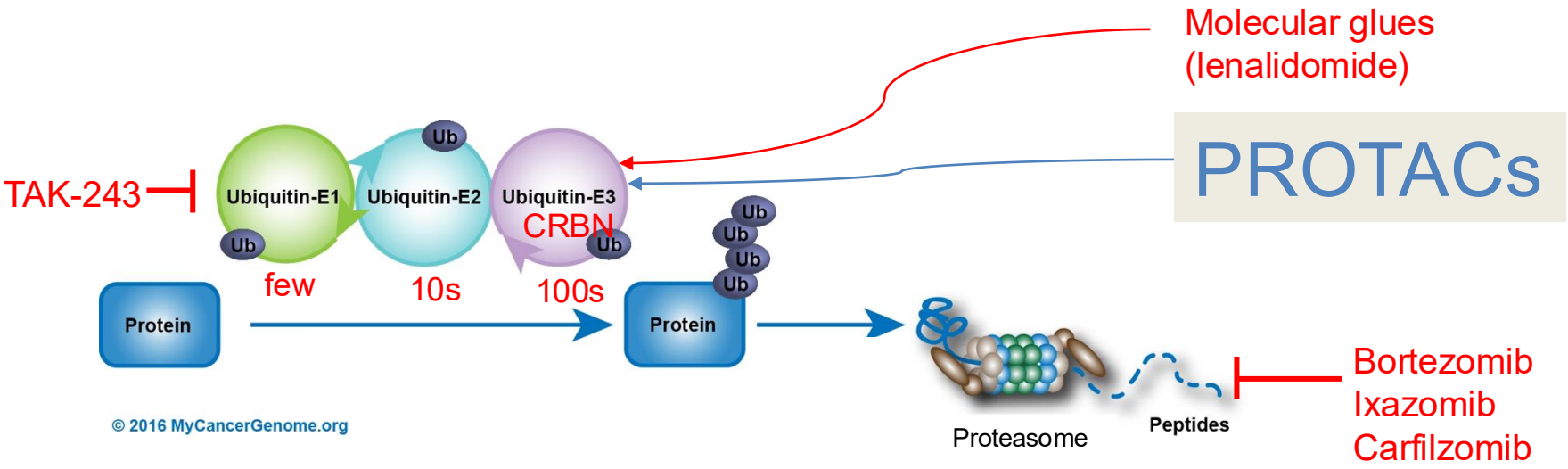
President:
P.L. Zinzani

Disclosures

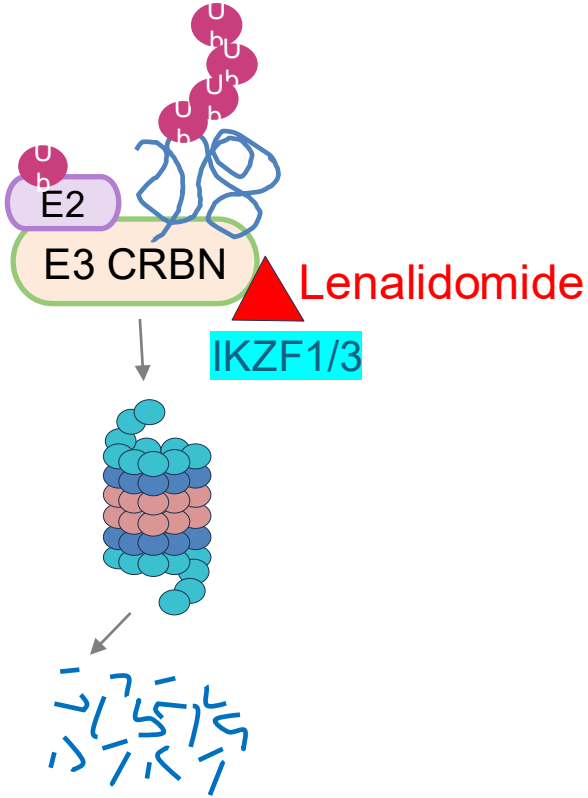
Disclosures of Alexey Danilov

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie	X		X				
AstraZeneca	X		X				
Beigene	X		X				
BMS	X						
GenMab	X		X				
Incyte	X						
Lilly Oncology	X		X				
Merck	X						
Nurix	X		X				
Regeneron	X		X				

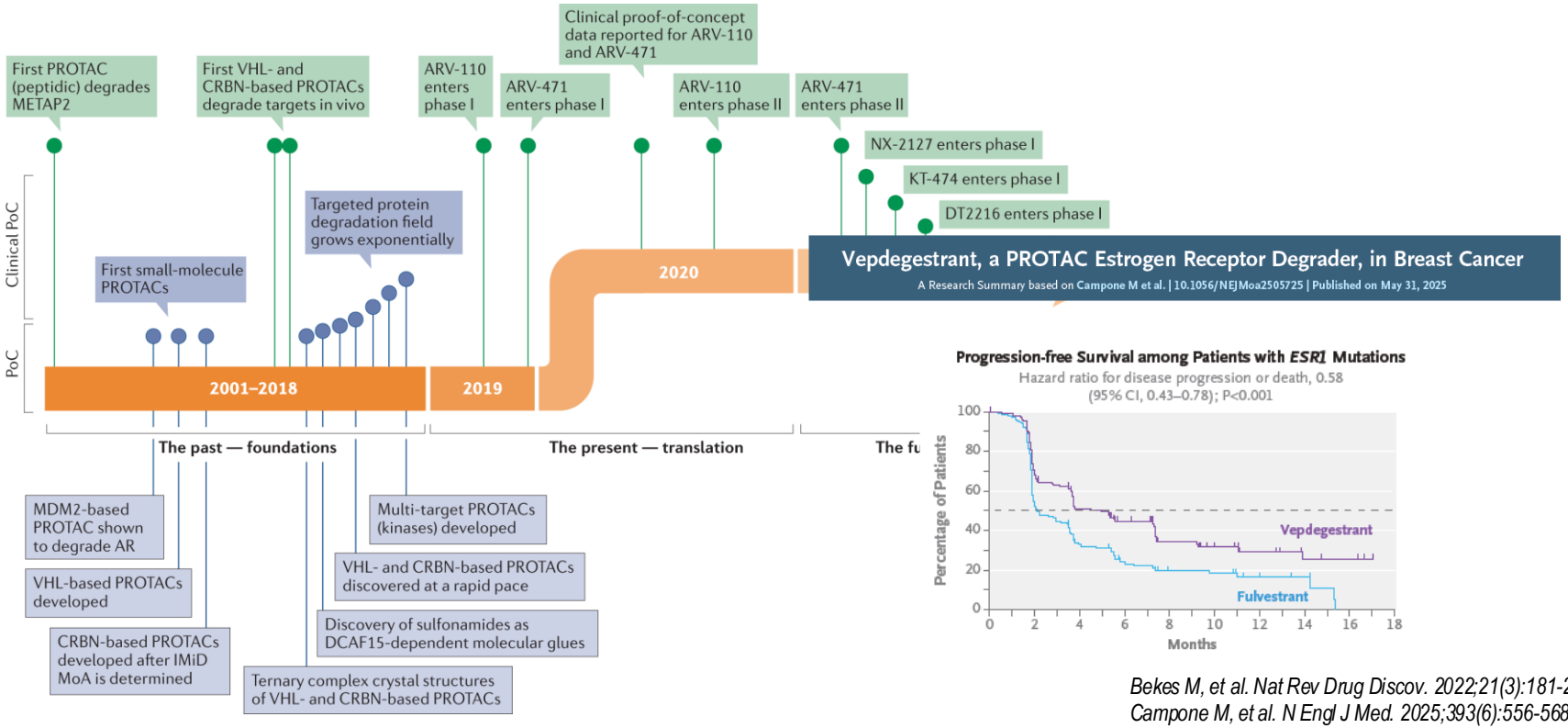
Drug Targets within the Ubiquitin-Proteasome System



Drug Targets within the Ubiquitin-Proteasome System



Timeline of PROTAC Development



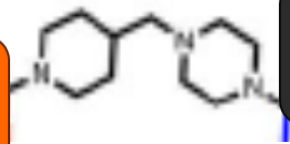
Bekes M, et al. Nat Rev Drug Discov. 2022;21(3):181-200.
Campone M, et al. N Engl J Med. 2025;393(6):556-568.

PROTACs: Hook and Harnesses

Kinases (BTK, BRAF, KRAS, IRAK, MEK, CDK, ALK, AKT)

Transcription factors (STAT)

Receptor proteins (AR, ER, EGFR)



VHL

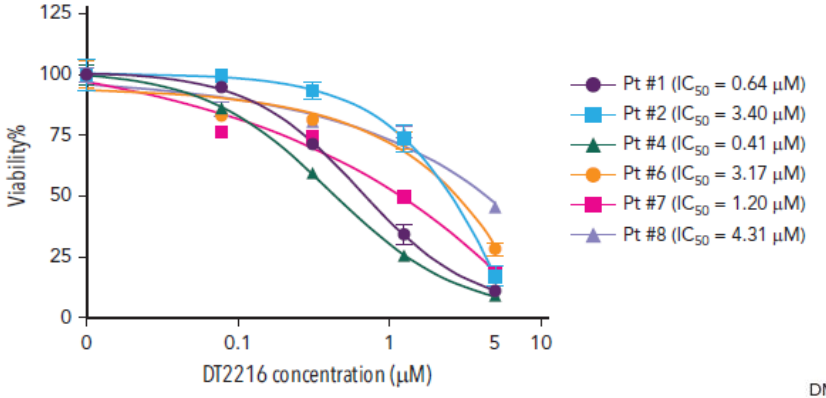
CRBN

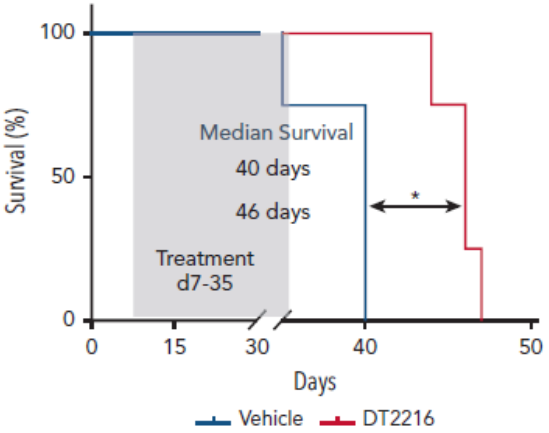
MDM2

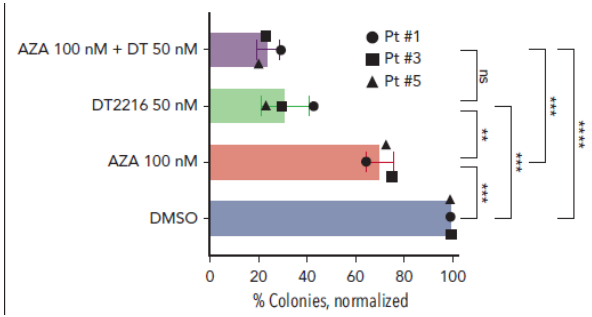
IAP

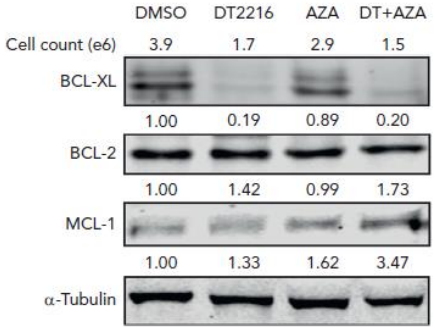
Huynh T, et al. Mol Cancer Ther. 2024;23(5):619-626.

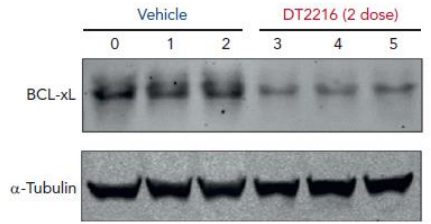
DT2216, a BCLX Degrader, Exhibits Anti-Leukemic Effect in AML Models





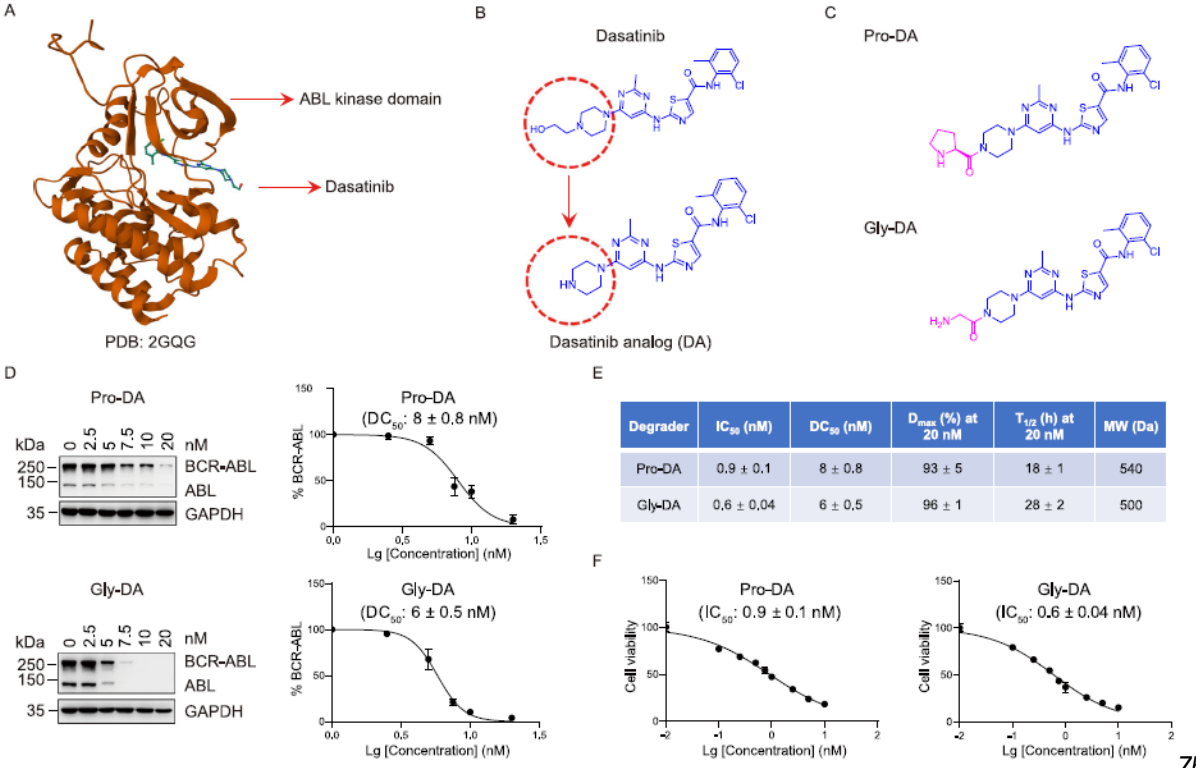






Wang Z, et al. Blood. 2025;146(3):341-355.

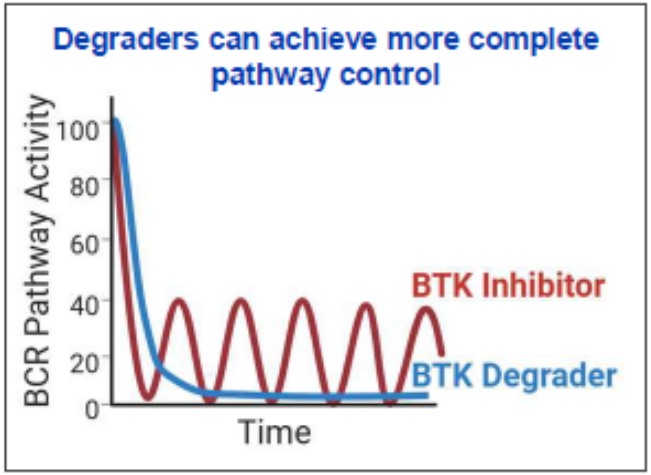
Dasatinib Analog, a Linker-free Bcr-Abl Degrader

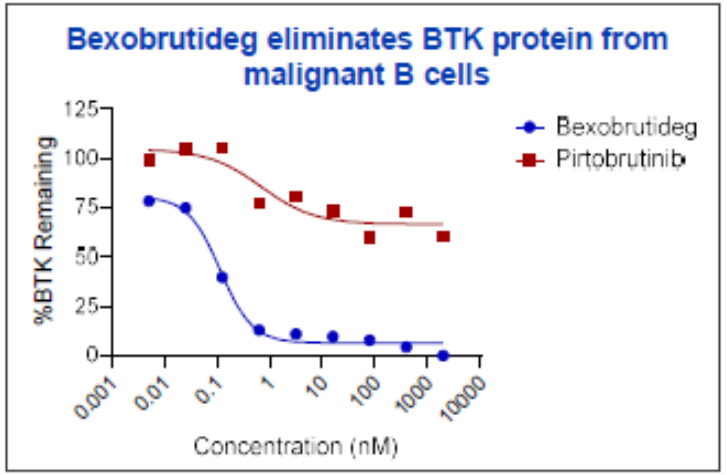


Degrader	IC_{50} (nM)	DC_{50} (nM)	D_{max} (%) at 20 nM	$T_{1/2}$ (h) at 20 nM	MW (Da)
Pro-DA	0.9 ± 0.1	8 ± 0.8	93 ± 5	18 ± 1	540
Gly-DA	0.6 ± 0.04	6 ± 0.5	96 ± 1	28 ± 2	500

Zhang J et al, Nature Comm 2025

Why We Think Degraders are Cool?

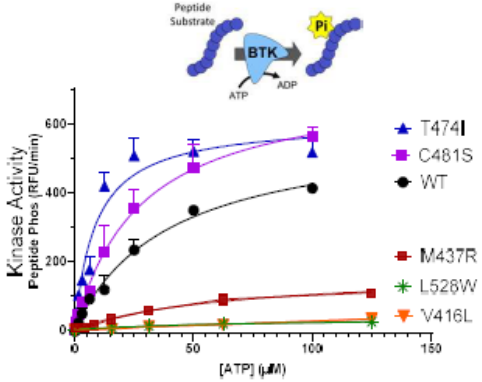




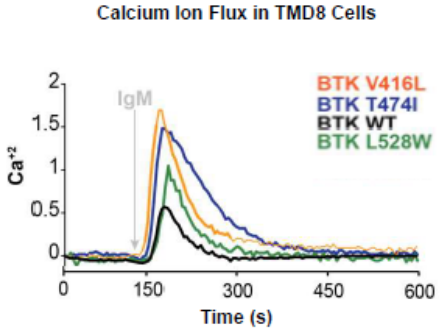
Slide credit: Nurix Therapeutics

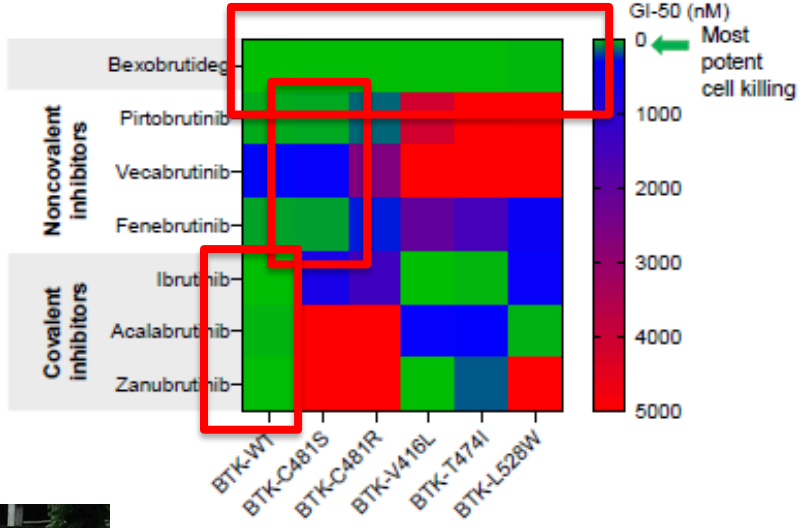
BTK Degraders: For All Your Anti-BTK Needs

BTKi-resistant mutations V416L and L528W lack kinase activity

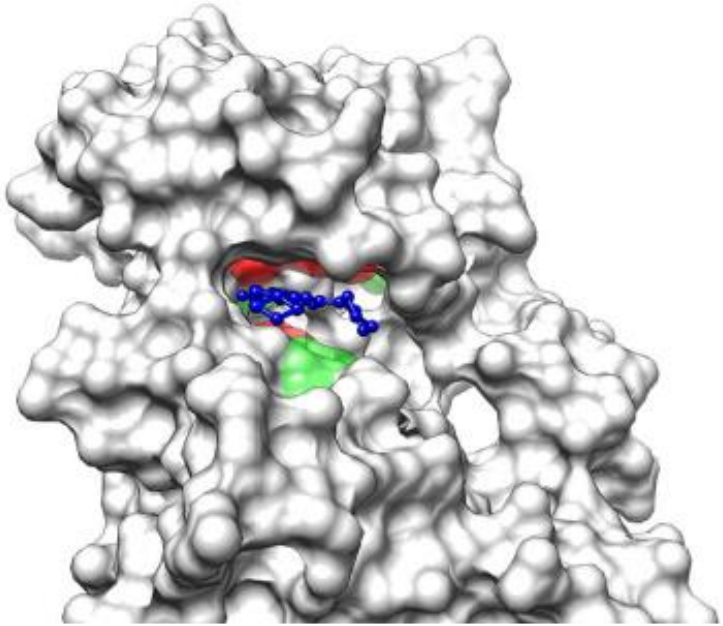


BTK kinase-dead mutations V416L and L528W propagate BCR signaling





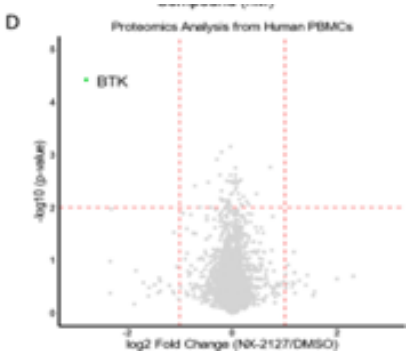
Bexobrutideg Binds in ATP Pocket Avoiding Interactions with Common Mutations



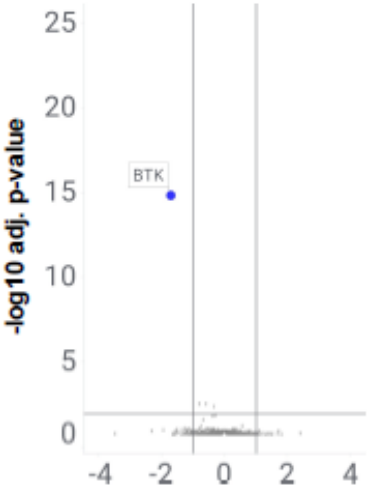
Slide credit: Nurix Therapeutics

BTK Degraders are Highly Selective Compounds

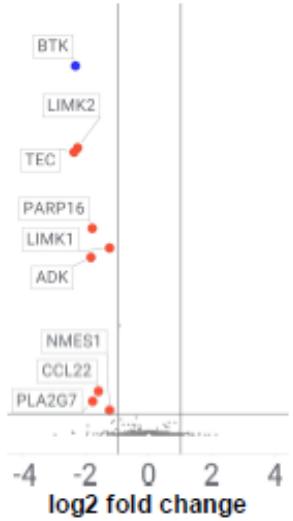
NX-2127



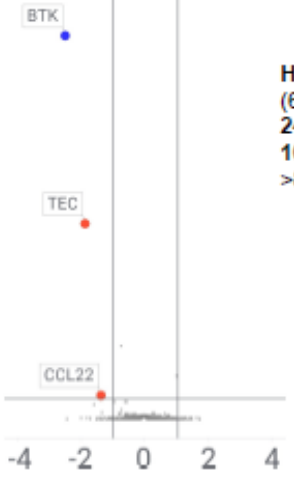
Bexobrutideg



BGB-16673



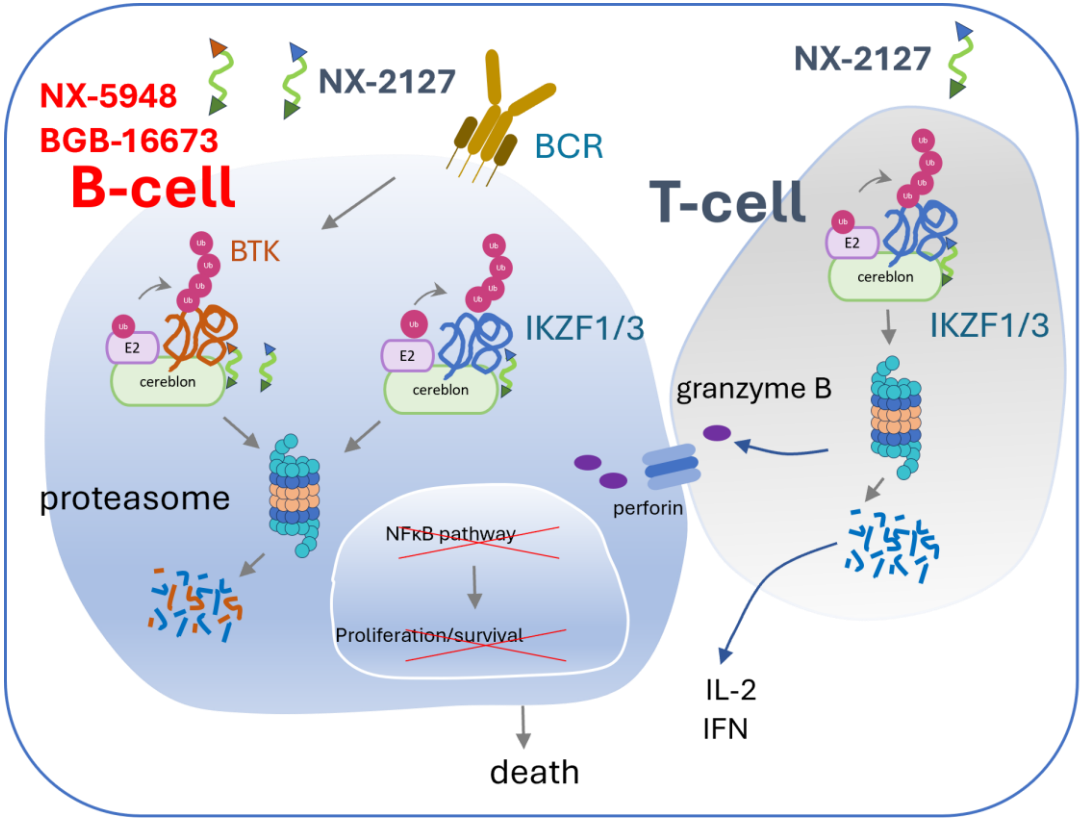
AbbVie cmpd. 1



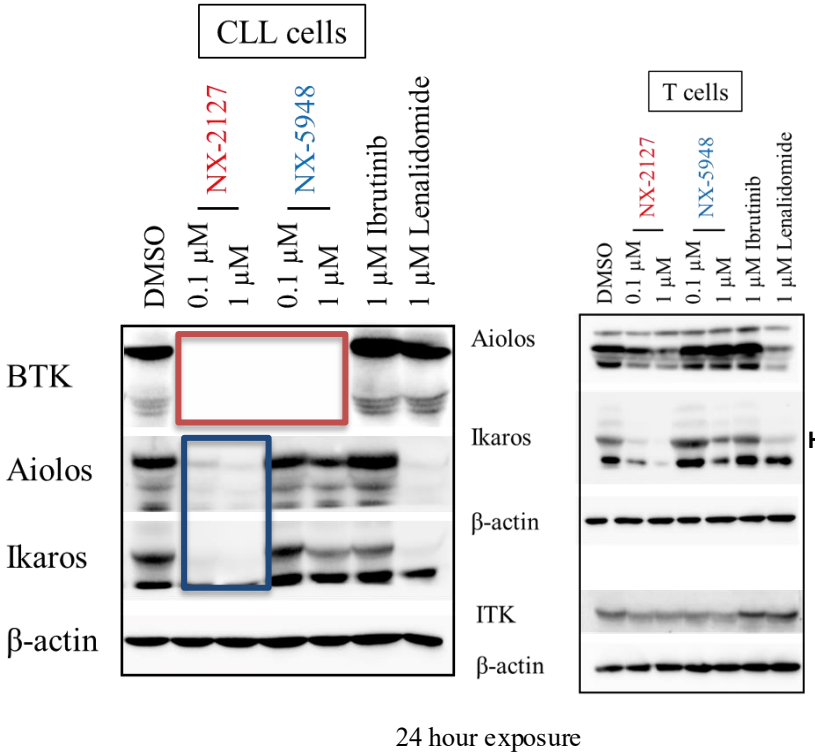
Human PBMCs
(6 healthy donors)
24-hour treatment
10xDC90
>8700 proteins detected

Robbins DW, et al. *J Med Chem*. 2024;67(4):2321-2336.
Noviski M, et al. Presented at: AACR; 2023. 2850.
Nurix Therapeutics

CRBN-recruiting dergaders NX-2127 (zelebrudomide), NX-5948 (bexobrutideg) and BGB-16673

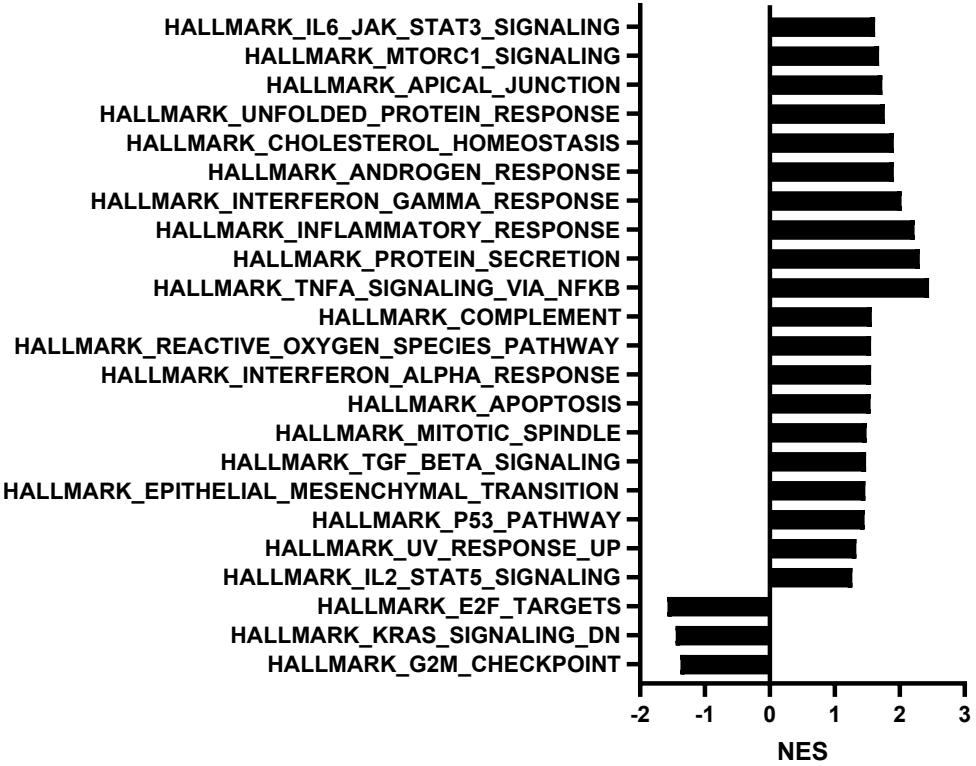


BTK and IKZF degradation by NX compounds



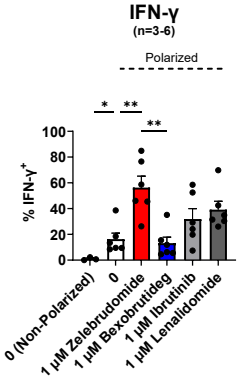
24 hour exposure

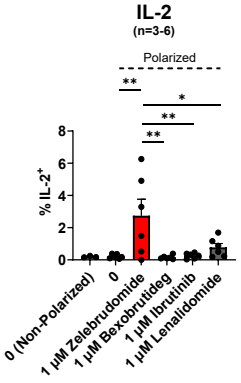
Zelebrudomide vs. Control (24h)

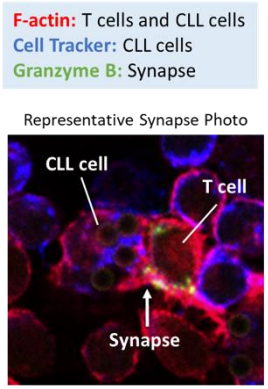


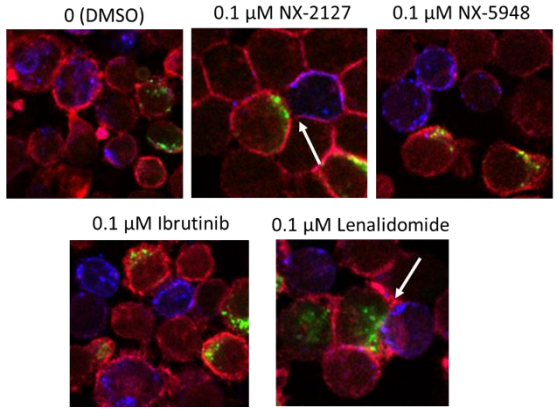
Huynh T et al, iwCLL 2025

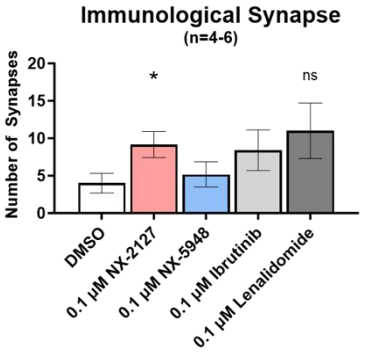
NX-2127 enhances synapse formation and cytotoxicity

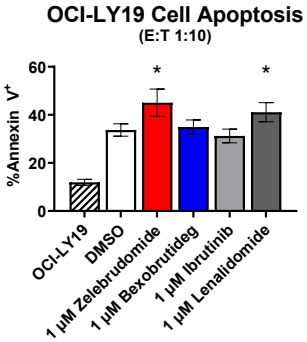








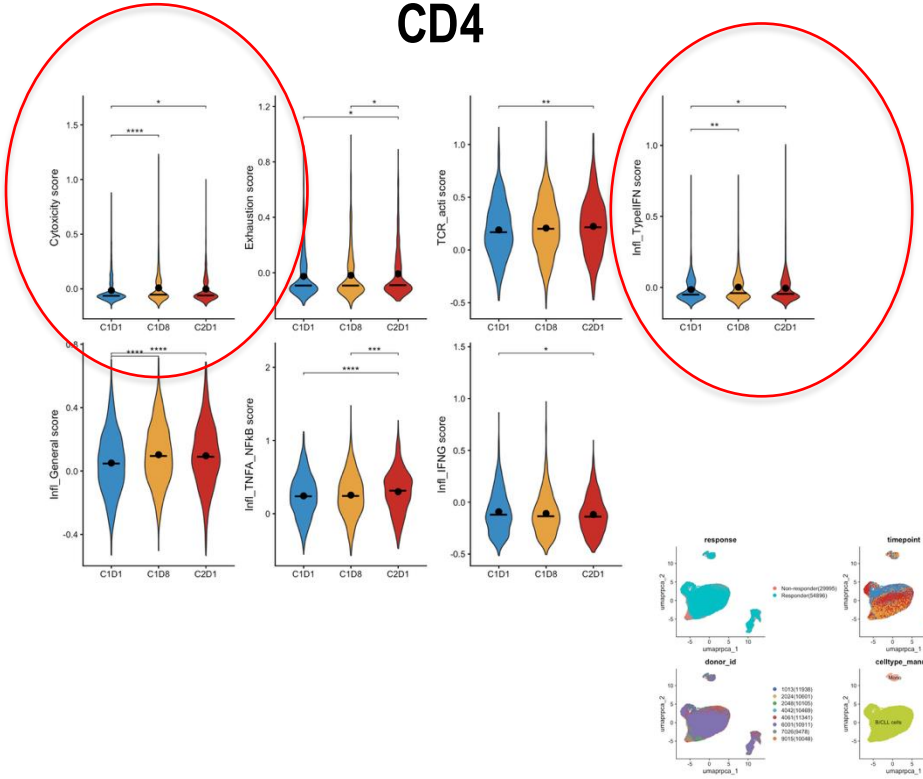




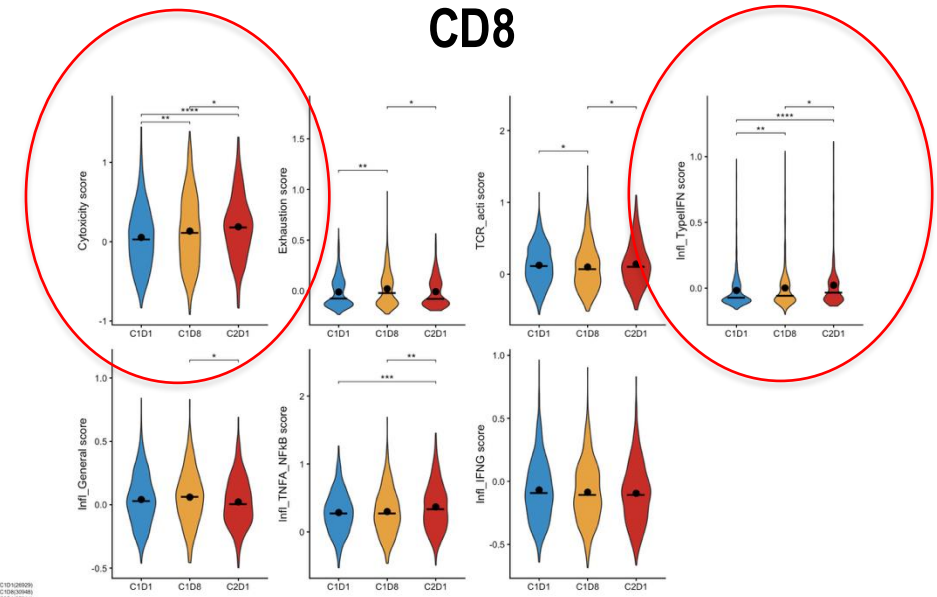
Huynh T et al, iwCLL 2025

Increased Cytotoxicity and IFN-γ Score in T cells from patients treated with NX-2127

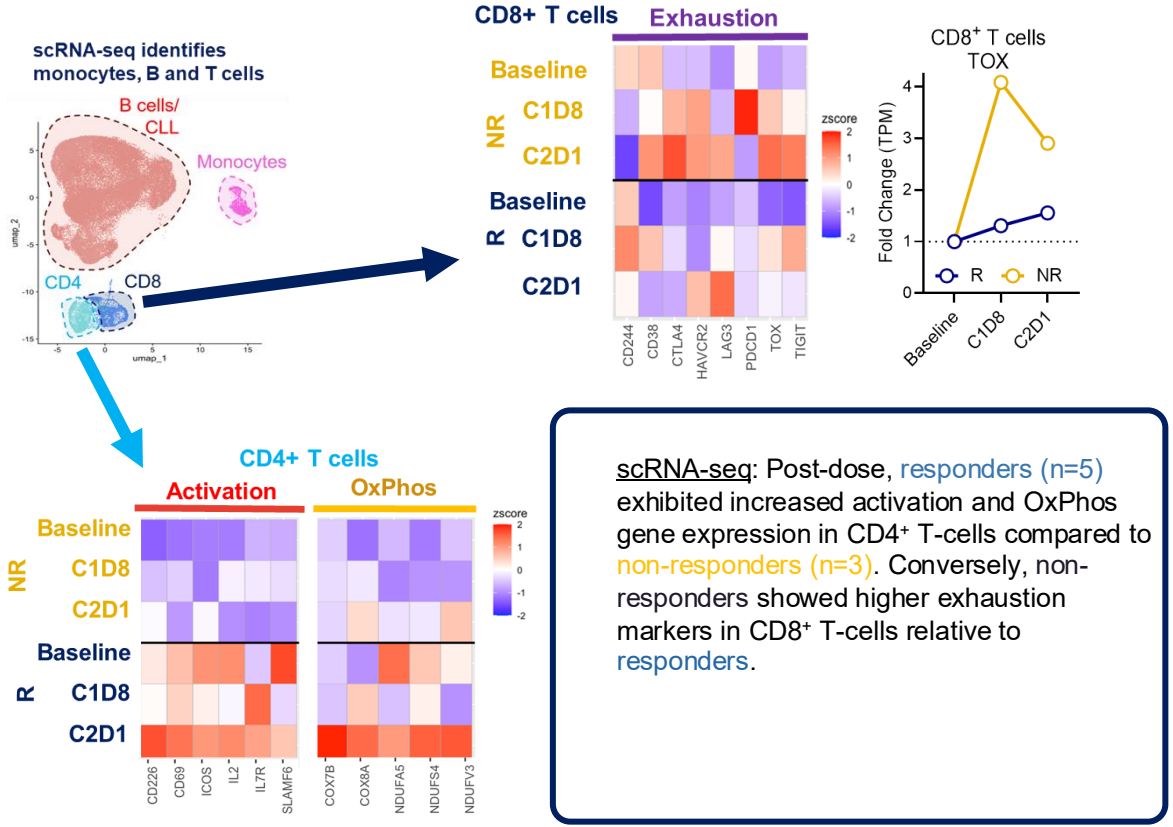
CD4



CD8



T cell signatures predict response to NX-2127



scRNA-seq: Post-dose, responders (n=5) exhibited increased activation and OxPhos gene expression in CD4+ T-cells compared to non-responders (n=3). Conversely, non-responders showed higher exhaustion markers in CD8+ T-cells relative to responders.

Bexobrutideg Phase 1a/b (NX-5948-301) Trial Design

Phase 1a/b clinical trial in adults with relapsed/refractory B-cell malignancies

Phase 1a dose escalation (fully enrolled)

CLL/SLL

- 600 mg QD
- 450 mg QD
- 300 mg QD
- 200 mg QD
- 100 mg QD
- 50 mg QD

CLL Phase 1b randomized cohort 1 (fully enrolled; 200 vs 600 mg)

- **CLL/SLL 200 mg QD** Prior BTKi and BCL2i
- **CLL/SLL 600 mg QD** Prior BTKi and BCL2i

CLL Phase 1b expansion, other cohorts (ongoing; all 600 mg)

- Non-C481S BTK mutations, prior BTKi and BCL2i
- Prior non-covalent BTKi, no BCL2i
- TP53 or 17p deletion, 2L, prior BTKi, no BCL2i
- 2L+, prior BTKi, no BCL2i
- BTKi-naïve
- With wAIHA, prior BTKi
- With CNS involvement, prior BTKi

WM/NHL

- 600 mg QD
- 450 mg QD
- 300 mg QD
- 200 mg QD
- 100 mg QD
- 50 mg QD

NHL/WM Phase 1b expansion cohorts (600 mg)

- **MZL** Marginal zone lymphoma
- **FL** Follicular lymphoma
- **WM** Waldenström macroglobulinemia
- **MCL** Mantle cell lymphoma
- **DLBCL** Diffuse large B-cell lymphoma
- **PCNSL** Primary CNS lymphoma

*2L+, second line +; **BCL2i**, B-cell lymphoma 2 inhibitor; **BTKi**, Bruton's tyrosine kinase inhibitor; **CLL**, chronic lymphocytic leukemia; **CNS**, central nervous system; **NHL**, non-Hodgkin's lymphoma; **QD**, once daily; **SLL**, small lymphocytic lymphoma; **wAIHA**, warm autoimmune hemolytic anemia; **WM**, Waldenström macroglobulinemia*

Demographics in Overall Population (Phase 1a/b)

Population representative of CLL/SLL demographics

Characteristics	Phase 1a/b – all patients (n=126)
Median age, years (range)	69.0 (35–88)
Sex, n (%)	
Female	42 (33.3)
Male	84 (66.7)
Ethnicity, n (%)	
Hispanic or Latino	5 (4.0)
Not Hispanic or Latino	114 (90.5)
Not reported	5 (4.0)
Unknown	2 (1.6)
Race, n (%)	
Black or African American	8 (6.3)
White	110 (87.3)
Not reported	7 (5.6)
Other	1 (0.8)

***CLL**, chronic lymphocytic leukemia; **SLL**, small lymphocytic lymphoma*

Data cutoff: 19 Sep 2025

Baseline Disease Characteristics in Phase 1a/b and 1a

Multiple prior lines of therapy and a high prevalence of baseline mutations

Characteristics	Phase 1a/b – all patients (n=126)	Phase 1a (n=48)
ECOG PS, n (%)		
0	45 (35.7)	19 (39.6)
1	81 (64.3)	29 (60.4)
CNS involvement, n (%)	5 (4.0)	5 (10.4)
Median prior lines of therapy, n (range)	3.0 (1–17)	4.0 (2–12)
Previous treatments,[a] n (%)		
BTKi	108 (85.7)	47 (97.9)
cBTKi	106 (84.1)	47 (97.9)
ncBTKi	34 (27.0)	13 (27.1)
BCL2i	78 (61.9)	40 (83.3)
BTKi and BCL2i	75 (59.5)	39 (81.3)
CAR-T therapy	9 (7.1)	3 (6.3)
Bispecific antibody	5 (4.0)	1 (2.1)
PI3Ki	26 (20.6)	14 (29.2)
Chemo/chemo-immunotherapies	84 (66.7)	35 (72.9)
Mutation status,[b] n (%)	(n=111)	(n=47)
BTK	44 (39.6)	18 (38.3)
TP53	44 (39.6)	21 (44.7)
PLCG2	9 (8.1)	7 (14.9)
BCL2	8 (7.2)	6 (12.8)

[a]*Patients could have received multiple prior treatments;* [b]*Mutations presented here were centrally sequenced*

***BCL2**, B-cell lymphoma 2; **BCL2i**, BCL2 inhibitor; **BTK**, Bruton's tyrosine kinase; **BTKi**, BTK inhibitor; **cBTKi**, covalent BTKi; **CAR-T**, chimeric antigen receptor T cell; **CNS**, central nervous system; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **ncBTKi**, non-covalent BTKi; **PI3Ki**, phosphoinositide 3-kinase inhibitor; **PLCG2**, phospholipase C gamma 2*

Data cutoff: 19 Sep 2025

Overall Safety Summary in Phase 1a/b 600 mg Group vs All Patients

Tolerable safety profile, consistent between the RP2D 600 mg and overall study population

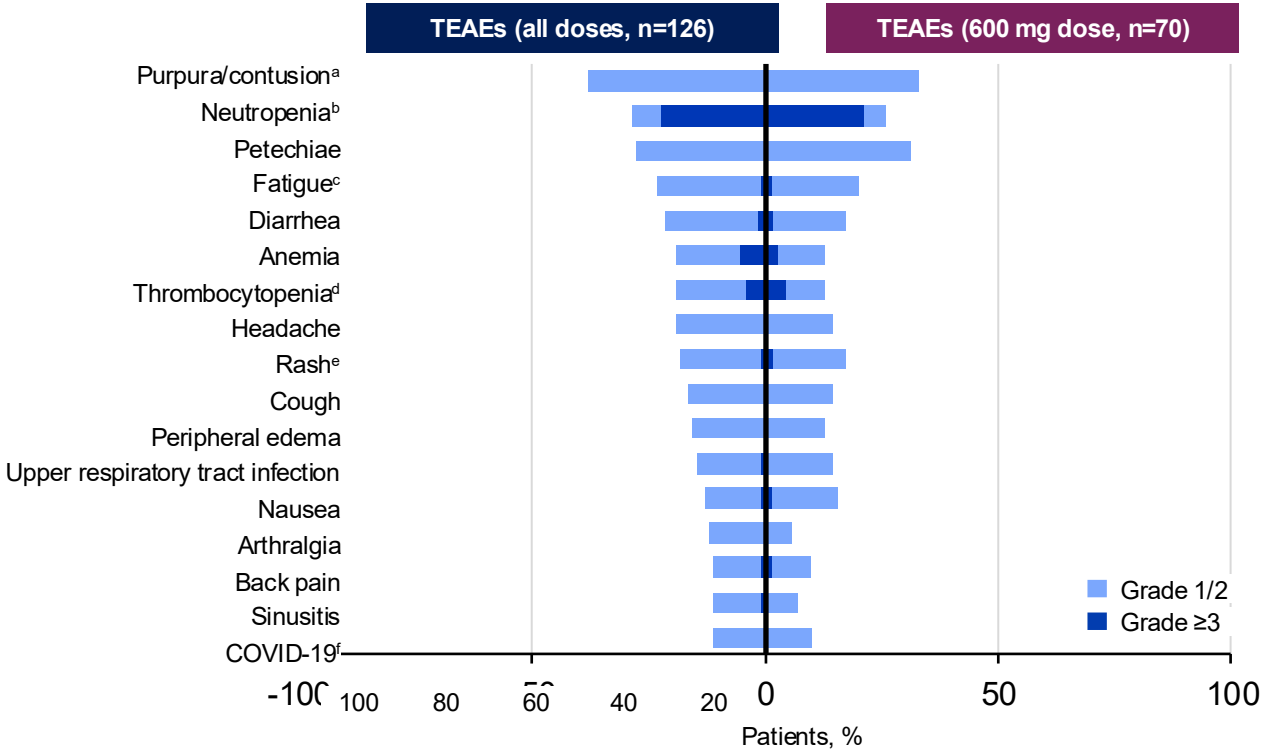
	Phase 1a/b – all patients (n=126)	Phase 1a/b 600 mg (n=70)
Any TEAE, n (%)	114 (90.5)	60 (85.7)
Treatment related	95 (75.4)	51 (72.9)
Grade ≥3	62 (49.2)	31 (44.3)
Treatment-related	31 (24.6)	18 (25.7)
SAE	27 (21.4)	10 (14.3)
Treatment-related	7 (5.6)	3 (4.3)
Grade 5[a]	3 (2.4)	1 (1.4)
Treatment-related	0	0
Leading to treatment discontinuation	8 (6.3)	4 (5.7)
Treatment-related	5 (4.0)	2 (2.9)
DLT	0	0
Median duration of treatment, months (range)	7.1 (0.0–32.3)	3.6 (0.0–18.0)

[a]*Grade 5 AEs: pulmonary embolism; death not otherwise specified; pneumonia*
***AE**, adverse event; **DLT**, dose-limiting toxicity; **RP2D**, recommended Phase 2 dose; **SAE**, serious AE; **TEAE**, treatment-emergent AE*

Data cutoff: 19 Sep 2025

TEAEs in ≥10% in Phase 1a/b 600 mg Group vs All Patients

Comparable AE profile for patients at the RP2D 600mg dose and overall population



- Tolerable safety profile consistent with prior disclosures
- No dose-limiting toxicities
- No systemic fungal infections or Grade 4 infections of any kind reported
- Single event of new onset atrial fibrillation in keeping with the rate in the age-matched general population
- 3 Grade 5 AEs (death not otherwise specified; pulmonary embolism; pneumonia; all deemed not related to bexobrutideg)

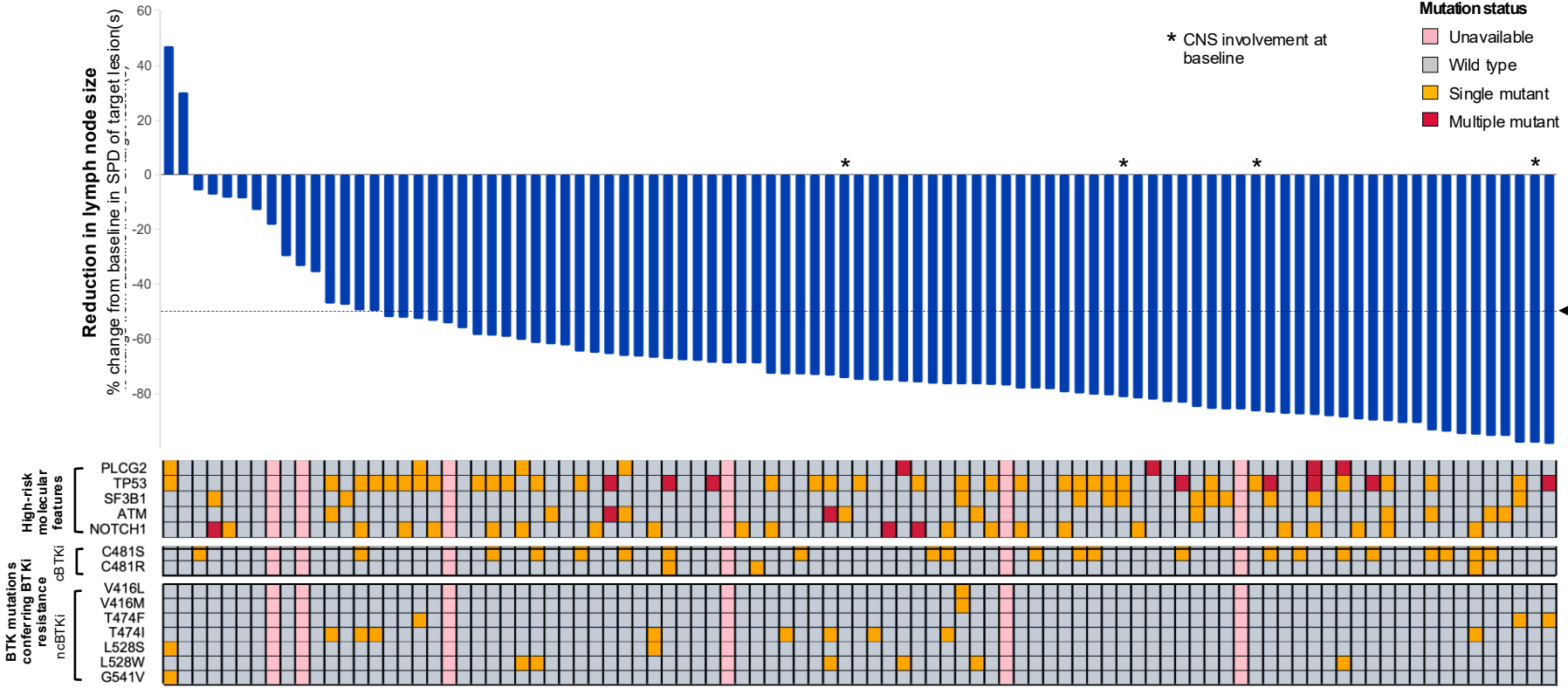
[a]Purpura/contusion includes episodes of contusion or purpura; [b]Aggregate of 'neutrophil count decreased' or 'neutropenia'; [c]Fatigue was transient; [d]Aggregate of 'thrombocytopenia' and 'platelet count decreased'; [e]Aggregate of 'rash' and 'rash maculopapular' and 'rash pustular'; [f]Aggregate of 'COVID-19' and 'COVID-19 pneumonia'

***AE**, adverse event; **NOS**, not otherwise specified; **RP2D**, recommended Phase 2 dose; **TEAE**, treatment-emergent adverse event*

Data cutoff: 19 Sep 2025

Reduction in Lymph Node Size in Phase 1a/b Overall Population[a]

Clinical activity across patients with BTK mutations,[b] high-risk molecular features and/or CNS involvement



[a]*Waterfall plot includes patients with measurable lymph node status (n=93); mutations were reported at VAF >5%;* [b]*Patients could have no mutations, a single mutation, or multiple mutations*
***ATM**, ataxia-telangiectasia mutated; **BTK**, Bruton's tyrosine kinase; **BTKi**, BTK inhibitor; **cBTKi**, covalent BTKi; **CLL**, chronic lymphocytic leukemia; **CNS**, central nervous system; **iwCLL**, International Workshop on CLL; **ncBTKi**, non-covalent BTKi; **NOTCH1**, neurologic locus notch homolog protein 1; **PLCG2**, phospholipase C gamma 2; **SPD**, sum of products diameters*

Data cutoff: 19 Sep 2025

Overall Response Rate in Phase 1a Across All Dose Levels (n=47)

Encouraging ORR and long median duration of response

Response-evaluable patients	Phase 1a (n=47)
Objective response rate (ORR),[a] % (95% CI)	**83.0 (69.2–92.4)**
Disease control rate (DCR),[b] % (95% CI)	95.7 (85.5–99.5)
Best response,[c] n (%)	
Complete response (CR)	2 (4.3)
Nodal partial response (nPR)	1 (2.1)
Partial response (PR/PR-L)	36 (76.6)
Stable disease (SD)	6 (12.8)
Progressive disease (PD)	2 (4.3)
Median follow-up,[d] months (range)	19.0 (13.5–32.3)
Median duration of response, months (95% CI)	20.1 (12.2–NE) (n=39)

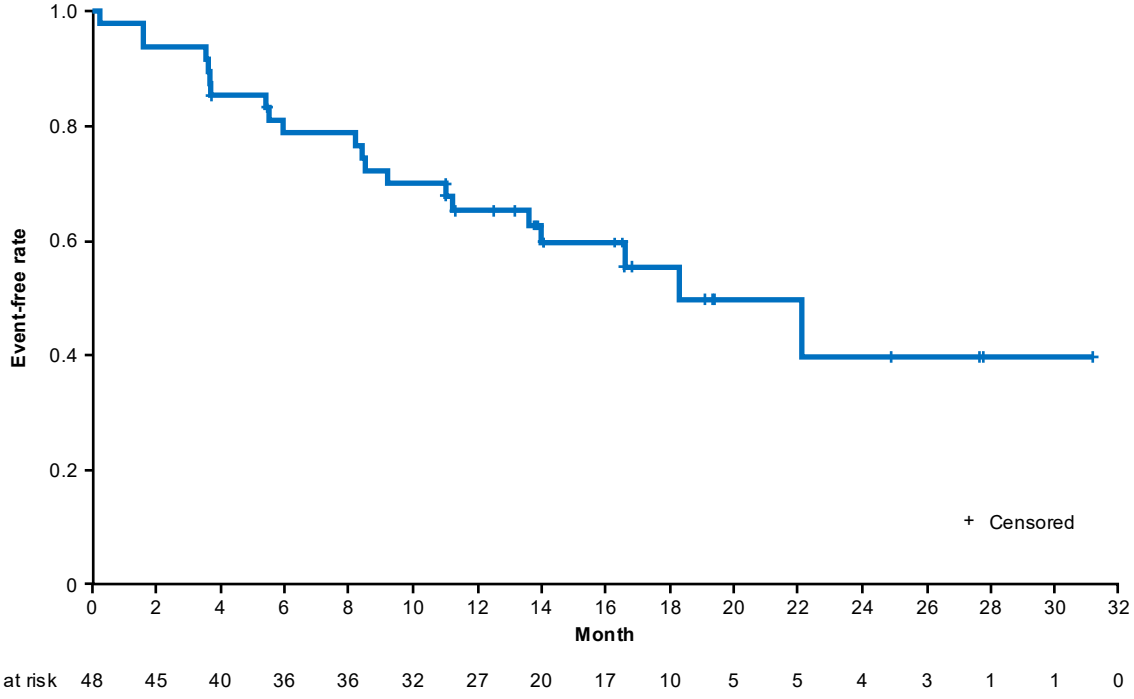
[a]Objective response rate includes CR + nPR + PR + PR-L; [b]Disease control rate includes CR + nPR + PR/PR-L + SD; [c]Percentages are based on the number of patients dosed who had at least one post-baseline disease assessment or documented clinical PD; [d]Time from treatment start to data cutoff

***CI**, confidence interval; **CR**, complete response; **DCR**, disease control rate; **NE**, not evaluable; **nPR**, nodal partial response; **ORR**, objective response rate; **PD**, progressive disease; **PR**, partial response; **PR-L**, partial response with lymphocytosis; **SD**, stable disease*

Data cutoff: 19 Sep 2025

PFS in Phase 1a Across All Dose Levels (n=48)

Median PFS of 22.1 months in study population with longest follow-up



PFS summary	
	n=48
Median PFS, months (95% CI)	22.1 (11.2–NE)
Median PFS follow-up, months (95% CI)	16.6 (14.0–19.3)

Median for PFS by Kaplan–Meier method; median PFS follow-up is by reverse Kaplan–Meier method; PFS data currently immature

Data cutoff: 19 Sep 2025

***CI**, confidence interval; **NE**, not evaluable; **PFS**, progression-free survival*

CaDAnCe-101: Phase 1/2, Open-Label, Dose-Escalation/Expansion Study in R/R B-Cell Malignancies

CaDAnCe-101 (BGB-16673-101, NCT05006716)

Key eligibility criteria

- Meets iwCLL 2018 criteria for treatment
- ≥2 prior therapies, including cBTKi if approved for their disease
- ECOG PS 0-2 (0-1 in the EU)
- Adequate organ function

Key objectives for part 1

- **Primary:** safety[c] and tolerability, MTD, and RDFE
- **Secondary:** PK, PD, and preliminary anti tumor activity[d]

Part 1: Monotherapy dose finding[a]

Part 1a: Dose escalation[b]
Selected R/R B-cell malignancies
(MZL, FL, MCL, CLL/SLL, WM, DLBCL, RT)
n≤72
Oral, QD, 28-day cycle
Doses: 50 mg, 100 mg, 200 mg, 350 mg, 500 mg, 600 mg

Part 1b: Safety expansion
Selected R/R B-cell malignancies
(MZL, MCL, CLL/SLL, WM)
n≤120

Part 1c: Additional safety expansion
Selected R/R B-cell malignancies
(MZL, WM, RT, DLBCL, FL)
n≤100

Part 1d: Additional safety expansion
R/R CLL/SLL
n≤30

Part 1e: Additional safety expansion
Selected R/R B-cell malignancies (Japan only)
(MZL, FL, MCL, CLL/SLL, WM)
n=6-9

Part 1f: Monotherapy safety expansion
Selected BTK inhibitor-naive B-cell malignancies
(MZL, MCL, CLL/SLL, WM, RT)
n≤40

Determination of BGB-16673 RDFE

Phase 2

- **Cohort 1:** Post-BTK inhibitor, R/R CLL/SLL
- **Cohort 2:** Post-BTK inhibitor, R/R MCL
- **Cohort 3:** Post-BTK inhibitor, R/R WM
- **Cohort 4:** Post-BTK inhibitor, R/R MZL
- **Cohort 5:** R/R FL
- **Cohort 6:** R/R non-GCB DLBCL
- **Cohort 7:** Post-BTK inhibitor, R/R RT

[a]Data from gray portions of the figure are not included in this presentation. [b]Treatment was administered until progression, intolerance, or other criteria were met for treatment discontinuation. [c]Safety was assessed according to NCI-CTCAE v5.0 in all patients and iwCLL hematologic toxicity criteria in patients with CLL. [d]Response was assessed per iwCLL 2018 criteria with partial response with lymphocytosis modification for CLL, and per 2014 Lugano criteria for SLL, with the first response assessment after 12 weeks of treatment.

cBTKi, covalent Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; GCB, germinal center B cell; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; MCL, mantle cell lymphoma; MTD, maximum tolerated dose; MZL, marginal zone lymphoma; PD, pharmacodynamics; PK, pharmacokinetics; QD, once daily; R/R, relapsed/refractory; RDFE, recommended dose for expansion; RP2D, recommended phase 2 dose; RT, Richter transformation; SLL, small lymphocytic lymphoma; WM, Waldenström macroglobulinemia.

Baseline Patient Characteristics

Heavily pretreated, with high-risk CLL features

	Total (N=68)
Age, median (range), years	70 (47-91)
Male, n (%)	47 (69.1)
ECOG PS, n (%)	
0	38 (55.9)
1	29 (42.6)
2	1 (1.5)
CLL/SLL risk characteristics at study entry, n/N with known status (%)	
Binet stage C	29/64 (45.3)
Unmutated IGHV	38/49 (77.6)
del(17p) and/or *TP53* mutation	46/68 (67.6)
Complex karyotype (≥3 abnormalities)	22/44 (50.0)

	Total (N=68)
Mutation status, n/N (%)	
BTK mutation present	26/66 (39.4)
PLCG2 mutation present	10/66 (15.2)
BTK and *PLCG2* mutation present	5/66 (7.6)
No. of prior lines of therapy, median (range)	4 (2-10)
Prior therapy, n (%)	
Chemotherapy	49 (72.1)
cBTK inhibitor	64 (94.1)
ncBTK inhibitor	14 (20.6)
BCL2 inhibitor	56 (82.4)
cBTK + BCL2 inhibitors	44 (64.7)
cBTK + ncBTK + BCL2 inhibitors	12 (17.6)
Discontinued prior BTK inhibitor due to PD, n/N (%)[a]	57/64 (89.1)

Data cutoff: August 22, 2025.

[a]The remaining 7 patients discontinued prior BTK inhibitor due to toxicity (n=4), and other (n=3).

BCL2, B-cell lymphoma 2; BTK, Bruton tyrosine kinase; cBTK, covalent Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; IGHV, immunoglobulin heavy chain variable region; ncBTK, noncovalent Bruton tyrosine kinase; PD, progressive disease; SLL, small lymphocytic lymphoma.

Overall Safety Summary

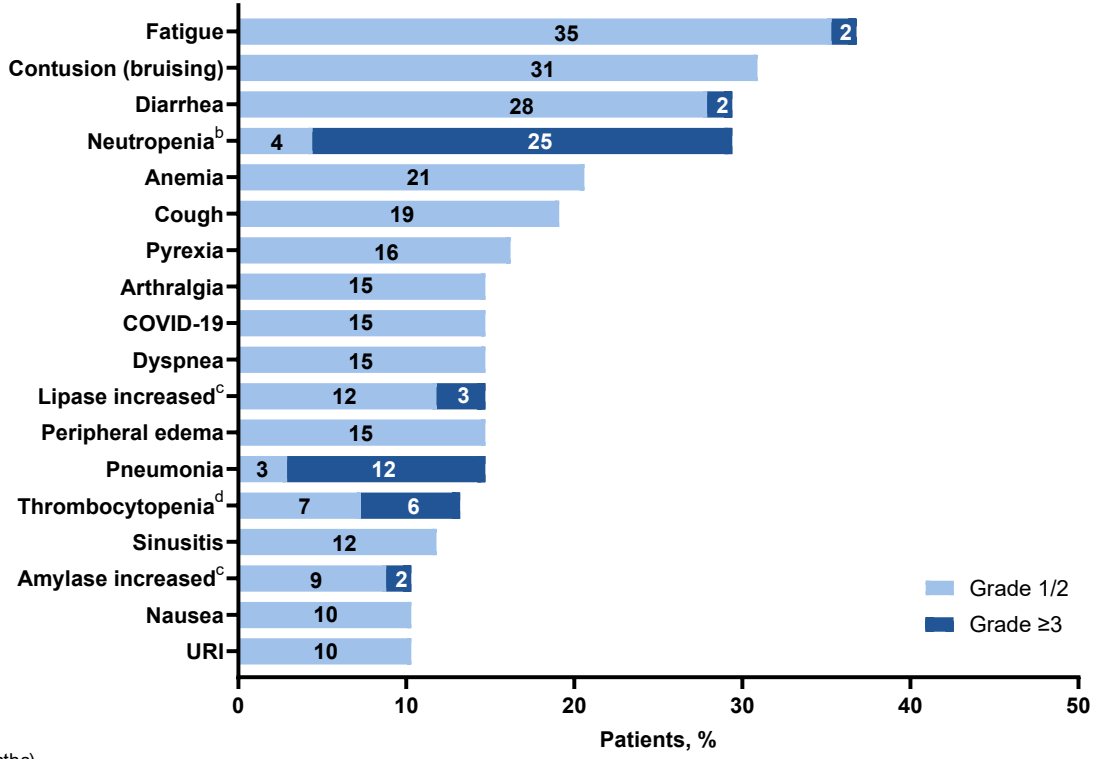
Tolerable safety profile, with no treatment-related TEAEs leading to death

Patients, n (%)	Total (N=68)
Any TEAE	65 (95.6)
Any treatment-related	52 (76.5)
Grade ≥3	42 (61.8)
Treatment-related grade ≥3	23 (33.8)
Serious	33 (48.5)
Treatment-related serious	9 (13.2)
Leading to death	5 (7.4)
Treatment-related leading to death	0
Leading to treatment discontinuation	12 (17.6)
Treatment-related leading to treatment discontinuation	3 (4.4)

Median study follow-up in safety-evaluable patients: 19.8 months (range, 0.3-34.0+ months).
TEAE, treatment-emergent adverse event.

Safety Summary and All-Grade TEAEs in ≥10% of All Patients

- Most common TEAEs were fatigue (36.8%) and contusion (bruising; 30.9%)
- Grade ≥3 neutropenia: n=17 (25.0%); 16 patients (23.5%) had grade ≥2 neutropenia at baseline
  - Neutropenic fever: n=1
- Atrial fibrillation: n=3 (grade 1, n=1; grade 2, n=2, all transient (2 of them lasting 1 day) in the context of infection and PD, assessed as unrelated to treatment)
- Treatment-related major hemorrhage[a]: n=2 (one grade 3 subdural hemorrhage and one grade 3 post-procedural hematuria)



Median follow-up in safety-evaluable patients: 19.8 months (range, 0.3-34.0+ months).

[a]Grade ≥3, serious, or any central nervous system bleeding. [b]Neutropenia combines preferred terms *neutrophil count decreased* and *neutropenia*. [c]All events were laboratory findings and were transient, mostly occurring during the first 1-3 cycles of treatment, with no clinical pancreatitis. [d]Thrombocytopenia combines preferred terms *platelet count decreased* and *thrombocytopenia*.

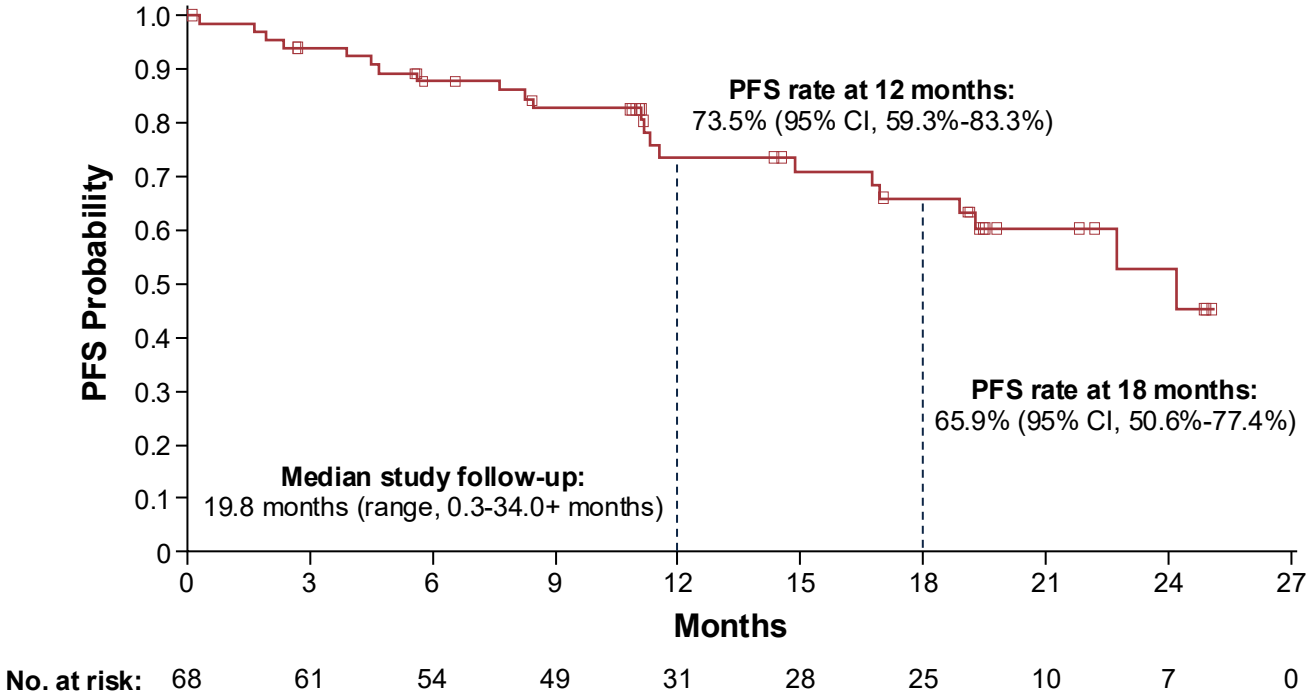
PD, progressive disease; TEAE, treatment-emergent adverse event; URI, upper respiratory tract infection.

Overall Response Rates in High-Risk Subgroups

Characteristic, n/N with known status (%)	ORR
Prior cBTKi + BCL2i	41/44 (93.2)
Prior cBTKi + BCL2i + ncBTKi	9/12 (75.0)
6 or more prior lines of therapy	13/16 (81.3)
del(17p) and/or *TP53* mutation	37/46 (80.4)
Complex karyotype (≥3 abnormalities)	16/22 (72.7)
***BTK* mutations**	20/26 (76.9)
***PLCG2* mutations**	9/10 (90.0)

BCL2i, B-cell lymphoma 2 inhibitor; cBTKi, covalent Bruton tyrosine kinase inhibitor; ncBTKi, noncovalent Bruton tyrosine kinase inhibitor; ORR, overall response rate.

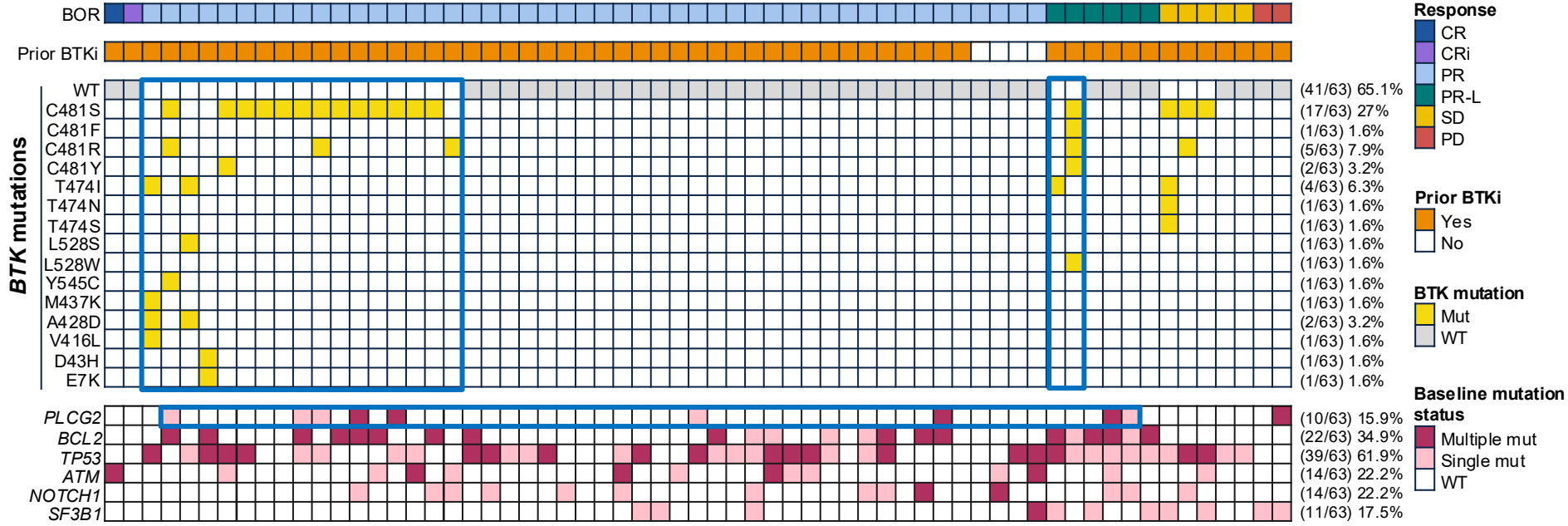
Progression-Free Survival



PFS, progression-free survival.

Responses Occurred Regardless of Specific Mutations

Best overall response vs baseline mutation[a]



[a]Genomic mutations were centrally assessed by targeted next-generation sequencing.

BTKi, Bruton tyrosine kinase inhibitor; BOR, best overall response; CR, complete response; CRi, complete response with incomplete marrow recovery; mut, mutation; PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease; WT, wild type.

Upcoming studies with BEXOBRUTIDEG

DAYBreak CLL-201

A Single-arm, Phase 2, Open-label Multicenter Study to evaluate NX-5948 in Adults with Relapsed/Refractory CLL/SLL Previously exposed to a BTKi and a BCL2i (NCT07221500)

Eligibility: prior cBTKi, ncBTKi and BCL2i
Primary Endpoint: ORR
Dose: bexobrutideg 600 mg po daily

Phase 3 confirmatory study (CLL-306): Bexobrutideg vs. Pirtobrutinib in 2L+ R/R CLL

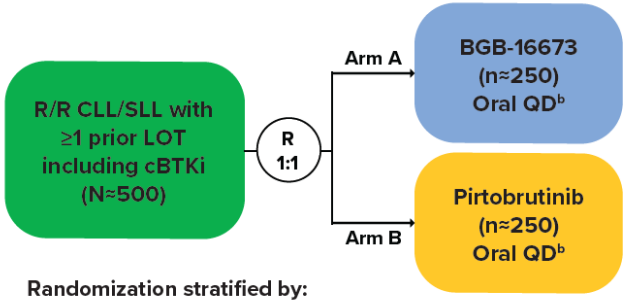
Eligibility: 2L+ including BTKi
Primary endpoint: PFS per IRC
Dose: Bexobrutideg 600 mg po daily

A Study to Evaluate the Safety and Efficacy of BGB-16673 Compared to Pirtobrutinib in Adults With Relapsed/Refractory CLL/SLL (CaDAnCe-304: NCT06973187)

Key eligibility criteria

- Age ≥18 years
- Confirmed CLL/SLL (iwCLL 2018 criteria)[9]
- R/R to ≥1 LOT[a] including a cBTKi
- Measurable disease by CT/MRI (SLL)
- ECOG PS of 0-2
- Adequate organ function
- No prior BTK protein degraders or ncBTKi

Study design



Randomization stratified by:

- Prior BCL2i
- del(17p) and/or *TP53* mutated
- Refractory to last cBTKi treatment

Objectives

Primary

- PFS (IRC)[c]

Secondary

- OS
- PFS (INV)[c]
- ORR (IRC/INV)
- PR-L or better rate (IRC/INV)
- DOR (IRC/INV)
- Time to next treatment
- Safety/tolerability[d]
- PROs

A Phase 3, Open-Label, Randomized Study of BGB-16673 Compared to Investigator's Choice in Patients With Relapsed/Refractory CLL/SLL Previously Exposed to Covalent BTK Inhibitors (CaDAnCe-303; NCT06970743)

R/R CLL/SLL :
- Prior exposure to cBTKi

N ≈ 150

Stratification:
- Age (>=65y or <65)
- Del(17p)/TP53
- Investigator's choice (BR/ HDMP+R /Clb.+Obi.)

R
1:1

Arm A (N≈75)
BGB-16673
200mg QD until IRC PD or intolerance

Arm B(N≈75)
Investigator's choice

BR
Bendamustine 90mg/m^2 IV, on D1 & D2 of C1-6
Rituximab 375 mg/m^2, IV, on C1D1; 500 mg/m^2, IV, on D1 of C2-6

OR

HDMP+R
Methylprednisolone 1 g/m^2, IV, d1-5 of C1-6
Rituximab 375 mg/m^2, IV, on C1D1; 500 mg/m^2, IV, on D1 of C2-6

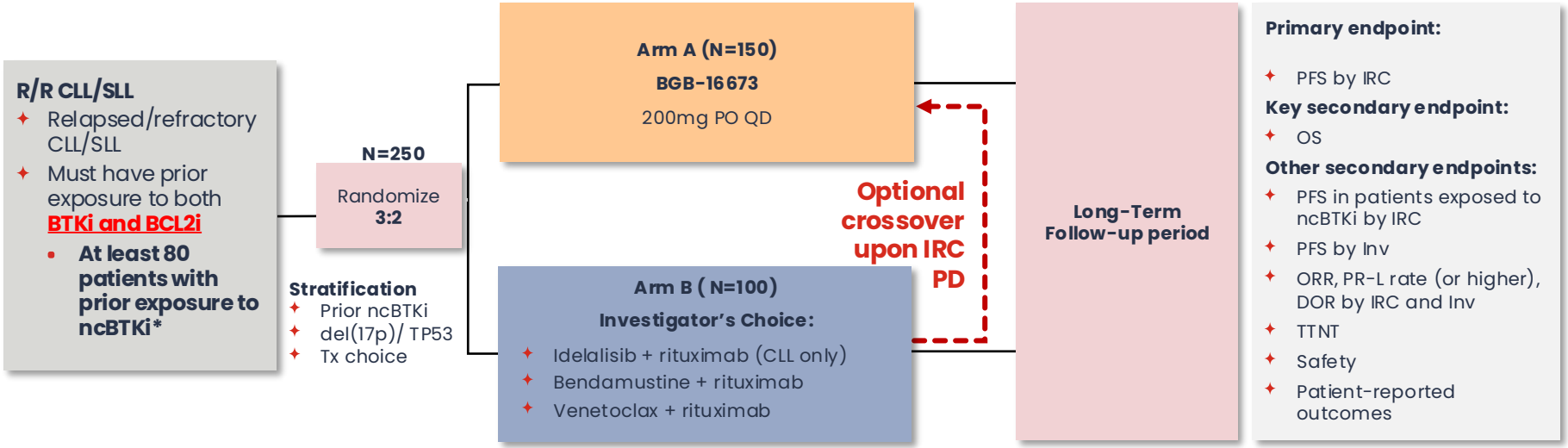
OR

Chlorambucil + Obinutuzumab
Chlorambucil 0.5mg/kg, oral, D1 & D15 of C1-6
Obinutuzumab 100 mg on D1 and 900 mg on D2 (or 1000mg on D1), 1000mg on D8 and D15 of C1; 1000mg on D1 of C2-6

Optional Cross-over upon PD by IRC

Post-treatment Follow-Up Period

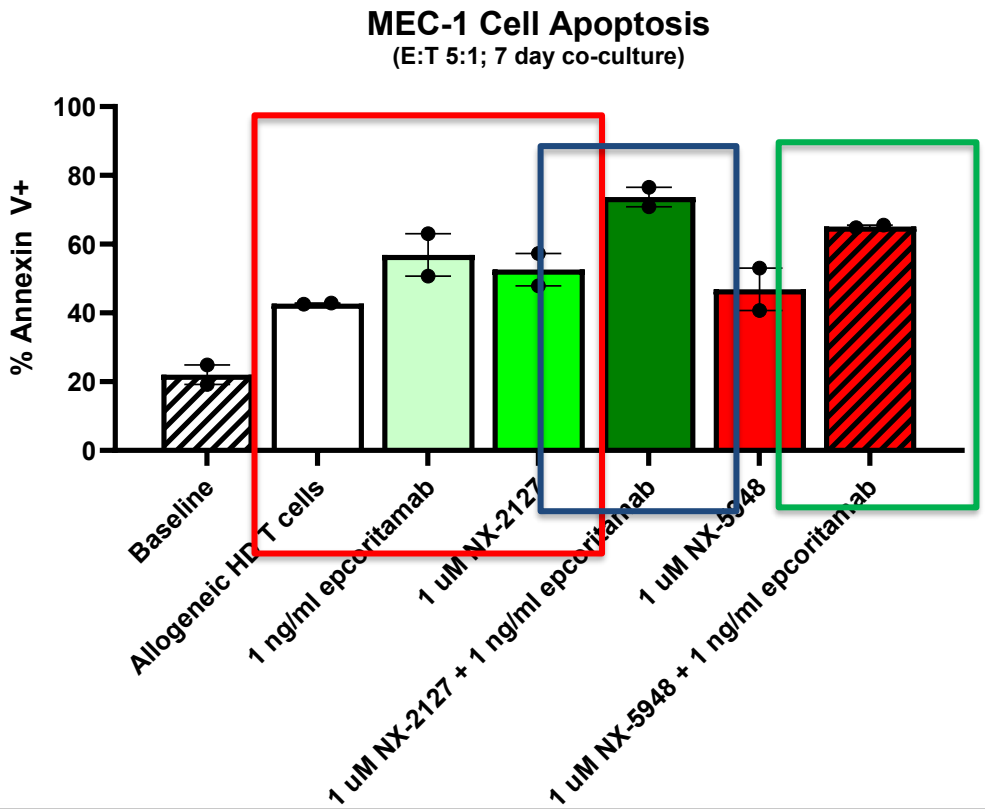
A Phase 3, Open-Label, Randomized Study of BGB-16673 Compared to Investigator's Choice in Patients With CLL/SLL Previously Exposed to Both BTK and BCL2 Inhibitors (CaDAnCe-302; NCT06846671)



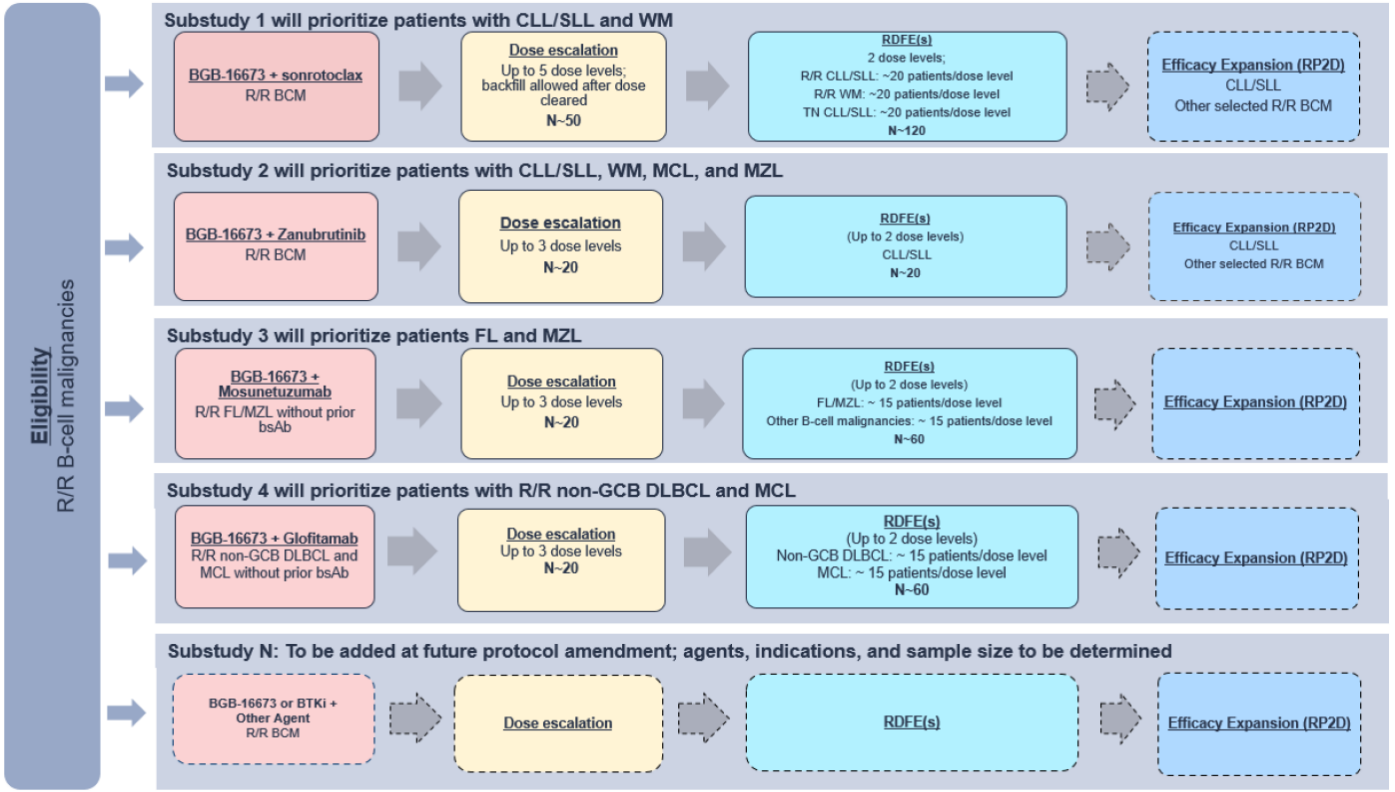
*In regions where an ncBTKi is approved and available and reimbursed, patients should have disease relapsed after or refractory to at least one line of therapy including an ncBTKi or been intolerant to a therapy with ncBTKi

- **In the US, sites must enroll triple exposed (prior cBTKi, ncBTKi, BCL2i) patients**

Degraders + bi-specifics



BGB-16673-104



Conclusions

Not all BTK degraders are created equal

They are highly effective in multiple-refractory patient population

Combinations are coming

Upcoming studies with BGB-16673

A Study to Evaluate the Safety and Efficacy of BGB-16673 Compared to Pirtobrutinib in Adults With Relapsed/Refractory CLL/SLL (NCT06973187)

Comparator Arm: Pirtobrutinib

Eligibility: 2L+ including BTKi

Primary endpoint: PFS per IRC

A Phase 3, Open-Label, Randomized Study of BGB-16673 Compared to Investigator's Choice in Patients With Relapsed/Refractory CLL/SLL Previously Exposed to Covalent BTK Inhibitors (CaDAnCe-303; NCT06970743)

Comparator Arm: BR or HDMP-R

Eligibility: 2L+ including BTKi

Primary endpoint: PFS per IRC

A Phase 3, Open-Label, Randomized Study of BGB-16673 Compared to Investigator's Choice in Patients With CLL/SLL Previously Exposed to Both BTK and BCL2 Inhibitors (CaDAnCe-302; NCT06846671)

Comparator Arm: Idelalisib-R or BR or Venetoclax-R retreatment

Eligibility: Prior BTKi and BCL2i

Primary endpoint: PFS per IRC